Predictability of hematopoietic stem cell transplantation rates

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ABSTRACT

Background and Objectives

Hematopoietic stem cell transplantation (HSCT) is a complex and expensive procedure. Trends in the use of this procedure have appeared erratic in the past. Information on future needs is essential for health care administrators.

Design and Methods

We analyzed the evolution of transplant rates, e.g. numbers of transplants per 10 million inhabitants, in Europe from 1990 to 2004 for all major disease categories and used Gross National Income (GNI) *per capita*, team density (numbers of teams per 10 million inhabitants) and team distribution (numbers of teams per 10,000 km^2) to measure the impact of economic factors in participating countries. Trends were compared by regression analyses, and countries were grouped by World Bank definitions into high, middle and low income categories.

Results

Transplant rates increased over time with nearly linear trends, in clear association with GNI *per capita* (R^2=0.72), and distinct by World Bank category within a narrow window of variation for both autologous HSCT (R^2=0.95, 0.98 and 0.94 for high, middle and low income categories, respectively) and allogeneic HSCT (R^2=0.99, 0.96 and 0.95 for high, middle and low income categories, respectively) when breast cancer (autologous) and chronic myeloid leukemia (allogeneic) were excluded. Team density (R^2=0.72) and team distribution (R^2=0.51) were also associated with transplant rates.

Interpretation and Conclusions

Transplant rates for HSCT in Europe are highly predictable. They are primarily influenced by GNI *per capita*. The absence of saturation and a nearly linear trend indicate that infrastructure lags behind medical needs. Isolated changes in single disease entities can easily be recognized.

Key words: predictability, HSCT rates.

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Hematopoietic stem cell transplantation (HSCT) is considered the treatment of choice for many patients with severe malignant or non-malignant, acquired or congenital disorders of the hematopoietic system or with chemosensitive, radiosensitive or immunosensitive tumors. HSCT has evolved over the last decades from an experimental procedure to the standard of care and is integrated into the treatment algorithm for many disease categories from diagnosis.[1-4] Better supportive care, increased donor pools and novel conditioning regimens have extended its use to new categories of patients and disease indications. However, HSCT is a high-cost procedure and can present a financial challenge for patients and health care systems in any country.[5-7] A correlation between the economic strength of individual countries and transplant rates, i.e. the number of transplants per number of inhabitants, was reported earlier by the European Group for Blood and Marrow Transplantation

(EBMT).[8,9] This correlation explained some of the differences in numbers of transplants between Eastern and Western European countries. Transplant rates were higher in countries with higher Gross National Income (GNI) or higher health care expenditures (HCE) *per capita*.

It is easy to understand that health care providers would like to have information on future needs. HSCT is a complex procedure, and is dependent on the availability of a specific infrastructure, trained medical personnel and support staff. Providing the infrastructure and its mandatory quality management requirements takes time and, therefore, at least short-term predictions are warranted.[10] This issue became first apparent with the sudden increase of autologous HSCT for breast cancer in the 1990s.[11,12] There was a massive increase of such transplants within a few years from nearly none to more than 5000 in Europe alone in 1996, followed by a similarly rapid decline. A similar phenomenon was observed a few years later with an increase and then rapid decrease in allogeneic HSCT for chronic myeloid leukemia in the late 1990s and the first few years of the new century. In 1999, chronic myeloid leukemia was the most frequent indication for an allogeneic HSCT worldwide. When imatinib mesylate, a specific inhibitor of the BCR/ABL tyrosine kinase, was introduced, transplant rates for chronic myeloid leukemia dropped and are still continuing to do so.[13-15] These two observations created the feeling amongst hospitals and health care institutions that transplant rates were erratic, rapidly changing and unpredictable. A fear of having *too much* infrastructure became prevalent.

Making use of its annual activity surveys, the EBMT made an attempt to gain insight into the mechanisms of the evolution in HSCT. Based on the data from 1990 to 2000, short-term predictions were attempted and extrapolations made in 2000 for the transplant rates in 2003.[16] These predictions were tested for their validity with the 2003 final data and extended throughout the observation period of the activity survey. The results of this analysis confirm the accuracy of the predictions made in 2000. They show that the changing usage of HSCT for breast cancer and chronic myeloid leukemia are the exception. As a rule, and adjusted for economic factors, transplant rates are highly predictable, increasing over time with nearly linear trends and in association with national income.There is no indication of saturation and the need for more infrastructure remains as urgent as before.

Design and Methods

Study design

This retrospective analysis was based on the prospective annual activity survey of the EBMT (*http://www.EBMT.org*) and was planned as a consequence of the report on short-term predictions for 2003 made in 2000.[16] In 1990, all EBMT members and affiliated teams were requested to report the numbers of patients they had transplanted in the previous year, providing information on the indication, stem cell source, and donor type.[17] Since 1991, collection of data was uniform and performed on an annual basis. Data were validated by the reporting team, which received a computer print-out of the entered data, and by cross-checking with national registries. The quality control program included on-site visits of selected teams. The EBMT survey now constitutes an integral part of a comprehensive quality assurance program, JACIE [Joint Accreditation Committee of the International Society for Cellular Therapy and EBMT (*http://www.jacie.org*)].

Transplant rates and disease selection

Transplant rates, i.e. the number of HSCT per 10 million inhabitants, were computed by disease indication and donor type for each country and for each year from 1991 to 2004 as previously defined,[8] for those indications for which more than 100 HSCT were performed in 2004, as listed in Table 1. Data are included on malignant and non-malignant diseases, autologous and allogeneic HSCT. Population data were obtained from the World Bank (*http://www.worldbank.org*). Transplant rates in this survey were not adjusted for patients who crossed borders and received their HSCT in another country.

Teams

Data from 143 teams in 20 European countries were included in the first report in 1990.[17] For the 2004 report, 612 teams in 38 European and 5 affiliated countries were contacted, of which 592 provided data.[18] This corresponds to a 97% return rate of active teams in 2004 and includes 481 of the 494 active EBMT member teams. In countries with national registries, we could ascertain that the numbers reported in the activity survey corresponded to the numbers of transplants performed within these countries. No major transplant team in Europe is missing from this list. It is estimated, from personal contacts, that the reported transplants include more than 90% of all autologous and more than 95% of all allogeneic HSCT. The teams are listed in the *Online Appendix* in alphabetical order according to country, city and EBMT center code. We received information that in 2004 no blood or marrow transplantations were performed in the following European countries: Albania, Andorra, Armenia, Georgia, Liechtenstein, Malta, Moldavia, Monaco, San Marino and the Vatican.

Economic factors

GNI *per capita* according to the World Bank definition was used to classify the participating countries

into high income (Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Portugal, Slovenia, Spain, Sweden, Switzerland, and United Kingdom), middle income (Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, and Slovakia) and low income countries (Azerbaijan, Belarus, Bosnia and Herzegovina, Bulgaria, Macedonia, Romania, Russia, Serbia and Montenegro, Ukraine and Turkey). The last category refers to the World Bank definition of *lower middle income* (*http://www.worldbank.org*). Data from 2004 were used for the trend analysis.

Data from non-European countries which traditionally participate in the EBMT activity survey (Algeria, Iran, Israel, Saudi Arabia, South Africa and Tunisia; *see appendix* and Gratwohl *et al.*)[18] were not included in the analysis. Iceland and Luxemburg were excluded because of missing data in some years which could not be corrected for in view of the small size of the countries. In order to deal with the changes as a consequence of the Balkan war, data from 1992 on only were used for the final analysis.

Team density and team distribution

In order to measure the impact of differences in numbers of transplant teams within a country compared to its population and its size, for each country we computed a team density, i.e. number of transplant teams per 10 million inhabitants, and team distribution, i.e. the number of transplant teams per 10,000 square kilometers, and looked for an association between transplant rates as defined above and team density or team distribution.

Statistical analysis

The annual numbers of hematopoietic stem cell transplantations (N) for each indication, each European country (c) and each World Bank (WB) category during the period from 1990 to 2004 were used to analyze trends in and predictability of such transplantations as well as to associate them with different factors. Transplant rates (TR) as defined above were computed for each year (y) and utilized for all analyses: as illustrated in Figures 1A and 2, a non-linear regression approach was chosen in order to describe the association between the transplant rates and the describing factors; y represents the dependent variable (transplant rates) and x the describing factors. C, d, b and a were estimated using the *ordinary least squares* method. The same formula was selected to compute a good fit of the model in Figure 1B.

Trends for several indication categories were then determined with linear regression analysis, again using the *ordinary least squares* estimation method. Together with the regression line and the coefficient of determination (R^2) we also computed the upper and lower 95% confidence intervals (see Figures 3 and 4).

Results

Numbers of transplants and main disease categories

In 1990, the total number of HSCT was 4234 of which 2137 were allogeneic (50%) and 2097 (50%) autologous HSCT. There was a marked increase over time in numbers of participating teams, countries and transplants. In 2004, the number of HSCT reported by all countries participating in the survey had risen to 22216: of these 7407 (33%) were allogeneic and 14809 (67%) autologous HSCT. Overall, there were 6711 allogeneic (32%) and 14329 (68%) autologous HSCT in those countries included in the predictability analysis for 2004. Table 1 details the increase over time and in absolute numbers for all transplants, for allogeneic transplants (Table 1A) and for autologous transplants (Table 1B). For all diseases, absolute numbers and transplant rates increased over time in all income categories. There were two main exceptions: (i) autologous transplants for breast cancer increased up to 1997, followed by a rapid decline thereafter; (ii) allogeneic HSCT increased for CML up to 1999 in all income categories, then numbers fell strongly, but primarily in high income countries (*see below*). There were additional minor non-linear aberrations in autologous HSCT with maximum numbers of autologus HSCT for ALL in 1998 and for AML in 2000.

GNI per capita and transplant rates

There was a clear association between transplant rates and GNI *per capita*, as illustrated by Figure 1. More transplants were performed in countries with a higher GNI *per capita*. The correlation was S-shaped with a wide variation (R^2=0.72) (Figure 1A). This association was found in all disease categories, for all donor types and all stem cell sources (*data not shown*). This association was observed over the whole time period. The same S-shaped association could be documented in those European countries with a rapid change in GNI *per capita* during the observation period, as illustrated by the example of Hungary (R^2= 0.98) (Figure 1B).

Team density, team distribution and transplant rates

Data showed a clear association between transplant rates and the organizational structure within a country (Figure 2). There was a clear association between World Bank income category and team density and team distribution (*data not shown*). In addition, a higher team density was associated with a higher transplant rate. This association was observed over the whole period. Transplant rates in Europe increased in parallel to the increase in team density over time (*data not shown*) and are illustrated for the year 2004 (Figure 2A). Data showed a similar, albeit weaker, association between team distribution and transplant rates (Figure 2B) with a higher transplant rate in countries with more teams per 10 000 km^2 (R^2=0.51).

Evolution of transplant rates

Transplant rates evolved during the whole observation period in a nearly linear fashion for allogeneic (Figure 3) and autologous (Figure 4) HSCT alike. This evolution showed a clear association with GNI *per capita*. It was significantly distinct by World Bank income category. There was a very narrow window of variation in all groups as documented by an R^2 of 0.99, 0.96 and, 0.95 for high, middle, and low income categories, respectively, for all allogeneic HSCT when those performed for CML were excluded (Figure 3A). This association was confirmed in single disease entities as illustrated for AML (Figure 3B) with a R^2 of 0.99 (high income), 0.95 (middle income), and 0.93 (low income). Similar rates were observed for the other disease categories (*data not shown*). The same was true for autologous HSCT (figures 4) with the same distribution between the high, middle and low income categories and a similar narrow window for all autologous HSCT when breast cancer was excluded (Figure 4A): R^2=0.95 (high income), 0.98 (middle income), and 0.94 (low income). The same was observed for single disease entities as illustrated for the most frequent indication, plas-

Table 1A. Evolution of HSCT in absolute numbers and transplant rates by disease indication and World Bank income category in Europe from 1990 to 2004. Allogeneic HSCT.

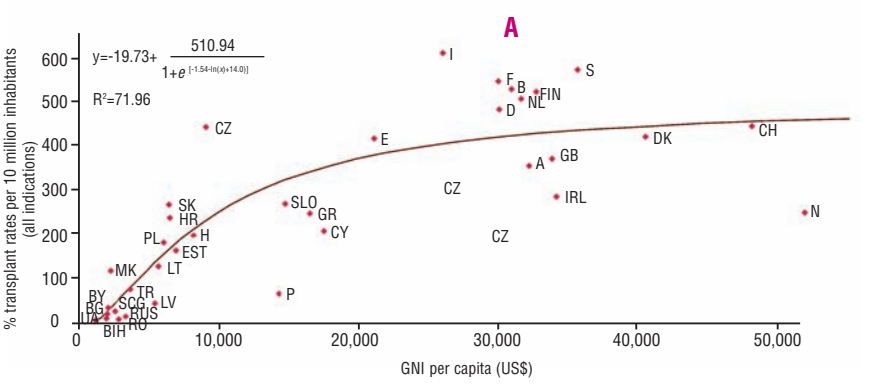
Disease group and World Bank income category	*1990*		*Peak*		*2004*	
	N	*TR*	*Year*	*N*	*N*	*TR*
Allogeneic HSCT						
All diseases			n.a.			
total	2137				6711	
high	2078	49.9			5820	139.7
middle	16	2.1			554	72.7
low	43	1.4			337	10.7
Acute myeloid leukemia			n.a.			
total	494				2212	
high	482	11.6			1954	46.9
middle	5	0.7			164	21.5
low	7	0.2			94	3.0
Acute lymphoblastic leukemia			n.a.			1256
total	489					
high	472	11.3			1080	25.9
middle	1	0.1			118	15.5
low	16	0.5			58	1.8
Chronic myeloid leukemia			1999			
total	540		1358		697	
high	522	12.5	1177	28.3	528	12.7
middle	7	0.9	115	15.1	98	12.9
low	11	0.3	66	2.1	71	2.2
Severe aplastic anemia			n.a.			
total	164				344	
high	156	3.7			267	6.4
middle	2	0.3			50	6.6
low	6	0.2			27	0.9
Thalassemia	n.a		n.a.		n.a.	
total						
high						
middle						
low						
Severe combined immunodeficiency			n.a.			
total	26				211	
high	26	0.6			180	4.3
middle	0	0.0			14	1.8
low	0	0.0			17	0.5

N: number of transplants; TR: transplant rates; year: year of maximum transplants; high: high income countries according to GNI per capita; middle: middle income countries according to GNI per capita; low: low income countries by GNI per capita; for details see text, methods section.

Table 1B. Evolution of HSCT in absolute numbers and transplant rates by disease indication and World Bank income category in Europe from 1990 to 2004. Autologous HSCT.

Disease Group and World Bank category	*1990*		*Peak*		*2004*	
	N	*TR*	*Year*	*N*	*N*	*TR*
Autologous HSCT						
All diseasess			n.a.			
total	2097				14329	
high	2071	49.7			12670	304.2
middle	5	0.7			1121	147.1
low income	21	0.7			538	17.0
Acute myeloid leukemia			2000			
total	388		1059		978	
high	375	9.0	897	21.5	839	20.1
middle	0	0.0	103	13.5	73	9.6
low	13	0.4	59	1.9	66	2.1
Acute lymphoblastic leukemia			1998			
total	289		369	218		
high	284	6.8	307	7.4	172	4.1
middle	1	0.1	53	7.0	36	4.7
low	4	0.1	9	0.3	10	0.3
Non-Hodgkin's lymphoma			n.a.			
total	486				4297	
high	485	11.6			3875	93.0
middle	0	0.0			312	40.9
low	1	0.03			110	3.5
Hodgkin's lymphoma			n.a.			
total	332				1478	
high	329	7.9			1162	27.9
middle	0	0.0			205	26.9
low	3	0.1			111	3.5
Multiple myeloma			n.a.			
total	130				5391	
high	130	3.1			4915	118.0
middle	0	0.0			326	42.8
low	0	0.0			150	4.8
Breast Cancer			1997			
total	0		2570		190	
high	0	0.0	2480	59.5	183	4.4
middle	0	0.0	80	10.5	1	0.1
low	0	0.0	10	0.3	6	0.2
Neuroblastoma			n.a.			
total	0				356	
high	0	0.0			286	6.9
middle	0	0.0			54	7.1
low	0	0.0			16	0.5

N: number of transplants; TR: transplant rates; year: year of maximum transplants; high: high income countries according to GNI per capita; middle: middle income countries according to GNI per capita; low: low income countries according to GNI per capita; for details see text, methods section.



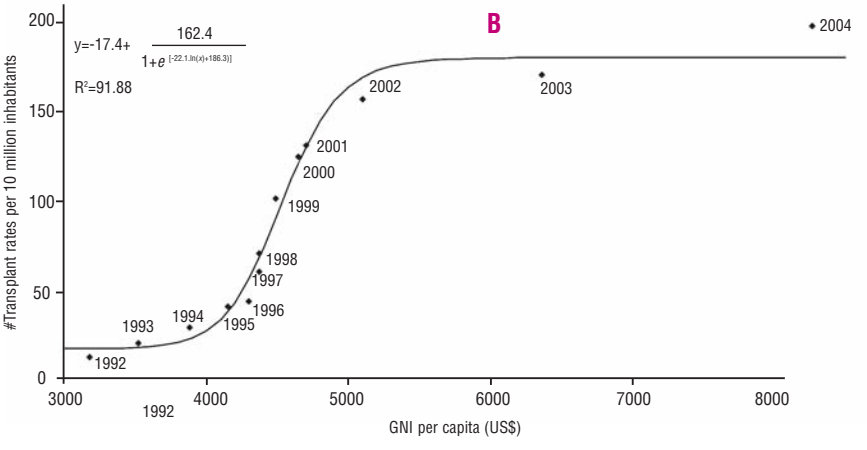
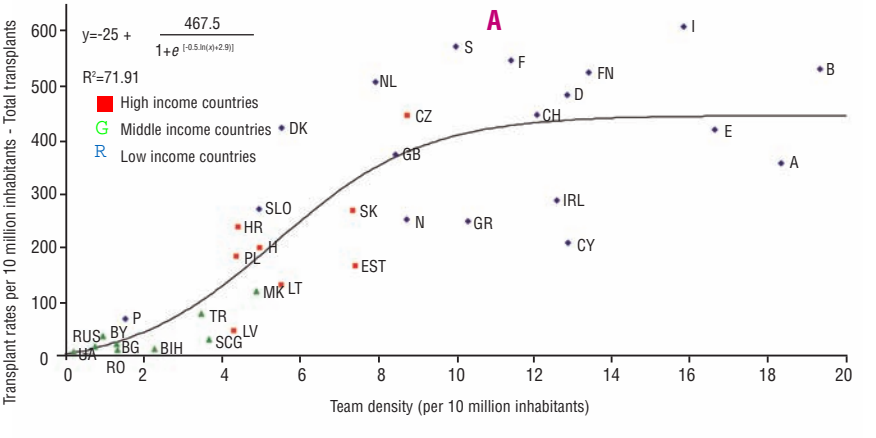


Figure 1. Associations between transplant rates and GNI *per capita* in European countries. (A) Association between transplant rates and GNI *per capita* for all countries, all indications and all donor types in 2004; (B) Association between transplant rates and GNI *per capita* over time in one European country: Hungary. Data points reflect transplant rates from 1992 to 2004.



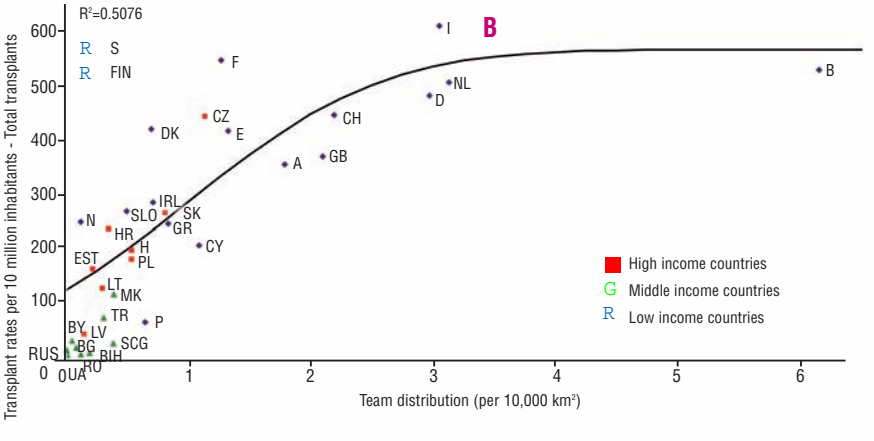


Figure 2. Association between transplant rates and team density and team distribution in Europe in 2004. (A) Association between transplant rates and team density in Europe 2004. (B) Association between transplant rates and team distribution in Europe 2004.

ma cell disorders (Figure 4B) (R^2=0.99, 0.97 and 0.83 for high, middle and low income categories, respectively).

There were the two initially described main exceptions. Transplant rates increased for allogeneic HSCT for CML up to 1999, after which they started to decline. This decline was more pronounced, as previously reported, in high income countries and similar transplant rates were observed in high and middle income countries in 2004.[21] Second, there was a massive increase of autologous HSCT for breast cancer up to 1997 with a similar rapid decline, in all income categories thereafter (Table 1).

Of special interest is the observation that transplant rates for autologous HSCT for Hodgkin's lymphoma increased more rapidly in middle income countries than anywhere else. As a consequence, similar transplant rates were noted in high and middle income countries in 2004 (Figure 4C).

Discussion

These data demonstrate that transplant rates in Europe are highly predictable, show a clear association with GNI *per capita* and are distinct in their evolution by World Bank income category. The rates of allogeneic and autologous HSCT for all major disease categories show no signs of saturation and increase with a very narrow margin of variation. These data are based on a 15-year observation period within the EBMT activity survey which covers about 90% of all autologous HSCT and more than 95% of all allogeneic HSCT carried out in Europe.[18] These data carry a clear message. HSCT is considered the treatment of choice[1,2] for several defined disease categories and, although transplant teams do their best to meet the needs, they still fail to do so. They are limited by resources, as illustrated by the clear association of transplant rates with GNI *per capita* and World Bank income category. They are also limited by the infrastructure, as documented by the association between transplant rates, team density and team distribution. Patients must have access to a transplant team in order to receive a transplant. This survey was not designed to determine what is the optimal infrastructure within a country. Still, the figures illustrate that probably one team per 1 – 2 million inhabitants and one team per 10,000 km^2 are reasonable targets.

There were two exceptions to the linear increase in HSCT during the observation period. There was the well known increase in autologous HSCT for breast cancer in the early 1990s and an equally rapid decline a few years later.[11,12] This pattern was based on spurious hopes and in part faked data and has been discussed at length in the medical literature.[12] The second exception, the increase in allogeneic HSCT for CML up to the year 1999 as well as the rapid decrease thereafter, is the result of new evidence. Allogeneic HSCT was the sole therapy with the potential for cure until to the introduction of imatinib mesylate. The introduction of a specific therapy with few immediate side effects and a track record of efficacy over a now 4-year-period has led to changes in recommendations and guidelines. Imatinib is now the first choice therapy for CML.[19,20] These observations underline that the evolution of HSCT is not erratic but predictable.

The data provided additional information. Transplant rates were associated with resources within a country and increased in a distinct pattern between countries with different economic backgrounds. This was reflected by the impact of GNI *per capita* and World Bank income category. Again, there were two exceptions. Transplant rates between high and middle income countries were found to have become similar for two diseases: allogeneic HSCT for CML and autologous HSCT for Hodgkin's lymphoma. There are various possible interpretations of these findings HSCT is a very expensive procedure. Nevertheless, in a cost-benefit analysis HSCT as a once in a life time procedure might compare favorably with a daily life-long expensive oral medication. Costs for imatinib are similar in all European countries; costs for HSCT vary substan-

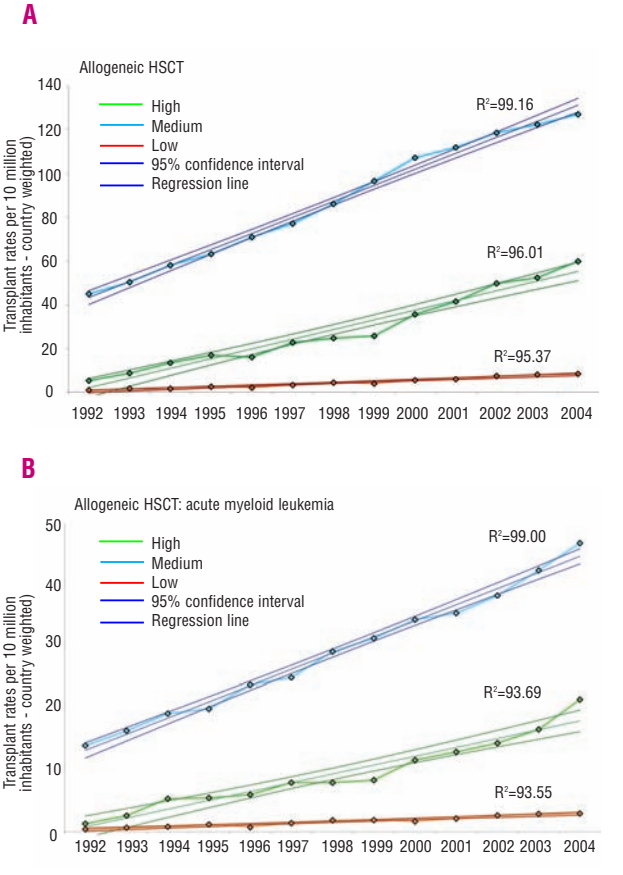


Figure 3. Evolution of transplant rates in Europe from 1992 to 2004. Allogeneic HSCT curves represent means and 95% confidence limits of weighted transplant rates according to World Bank income classification. (A) all allogeneic transplants (excluding those for chronic myeloid leukemia); (B) acute myeloid leukemia.

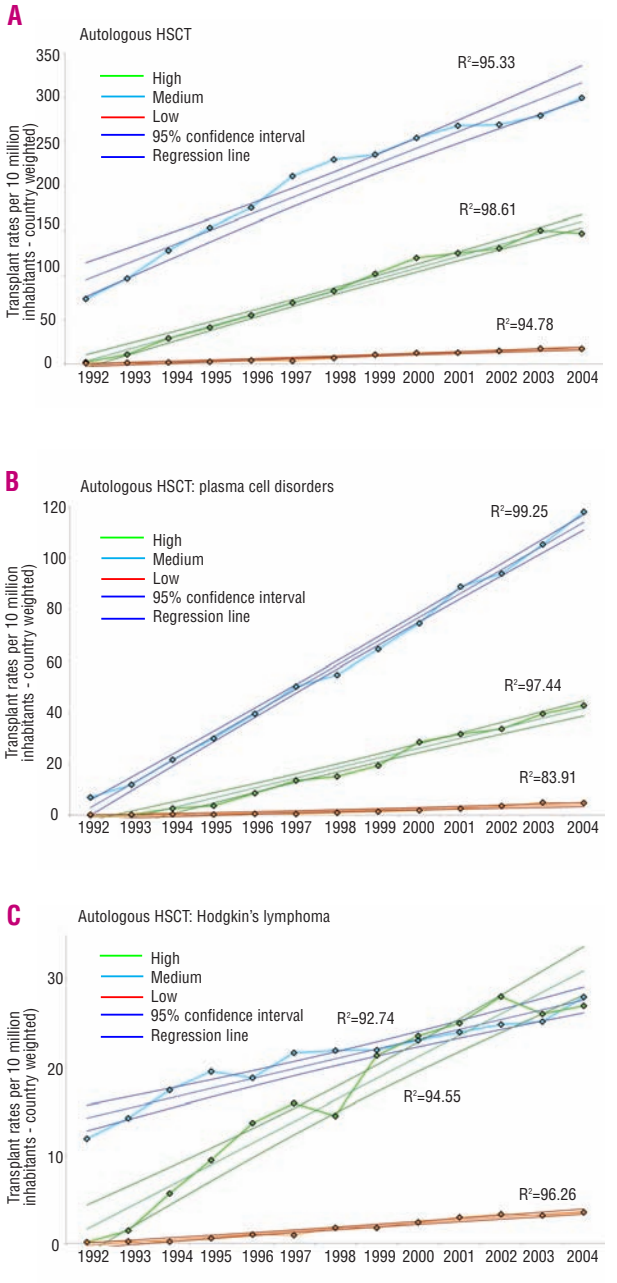


Figure 4. Evolution of transplant rates in Europe from 1992 to 2004. Autologous HSCT. Curves represent means and 95% confidence limits of weighted transplant rates according to World Bank classification (A) all autologous HSCT (excluding those for breast cancer); (B) plasma cell disorders, autologous; (C) Hodgkin's lymphoma, autologous.

tially between high and middle income countries, as was recently discussed.[21,22] The same applies to repetitive cycles of costly novel chemotherapeutic drugs or monoclonal antibodies for Hodgkin's lymphoma. It is highly likely that such considerations will have an even stronger impact in the future for countries in the middle income category when modern expensive therapies such as iron chelation in thalassemia or antibody treatment in paroxysmal nocturnal hemoglobinuria will have to be compared with HSCT.[21-27]

Our analysis has some limitations. Firstly, there is no uniform database on the incidence or prevalence of the individual disease categories in European countries. This was discussed previously[8,10,16] and cannot be corrected for. Still, it is unlikely that a change in incidence of a certain disease could have been responsible for the two main deviations from the common trend, breast cancer and chronic myeloid leukemia. Secondly, data are limited to Europe and it is difficult to extrapolate the conclusions to other continents. Nevertheless, it is likely that similar factors, such as GNI *per capita* and team density affect transplant rates. It is also likely that considerations on cost-effectiveness will affect decisions between HSCT and lifelong expensive therapies in non-European countries as well.[22]

What is the message of this report? It is clear that the need for HSCT is likely to continue to increase in the near future. Increasing donor pools worldwide, increasing availability of cord blood products and novel conditioning regimens will provide access to HSCT for patients previously not considered as candidates for this procedure.[2] Health care providers in European countries are faced with this complex problem and they should initiate concerted actions to put the infrastructure in place. This set of problems was discussed years ago.[28] Free market systems are most likely not ideal to provide the solution. It is important to find the correct balance between a restricted number of teams, in order that they have sufficient expertise, and an adequate number in order to guarantee access for all patients, independently of travel distances. It is obvious that solutions might be different in countries with geographically homogeneous or diverse regions. Above all, there is no indication of an abundance of transplant beds. There is not a need to restrict but rather to provide infrastructure. Health care agencies can be reassured that trends, with the advent of novel therapies which render HSCT superfluous, are rapidly recognized. However, cost considerations between a once-in-a-lifetime procedure and prolonged therapy are likely to increase needs in the future.[29]

In summary, the EBMT data document that the evolution of transplant rates is not erratic. These rates can be predicted accurately. With an up-to-date instrument, such as the EBMT activity survey, changes in therapy can easily be recognized at an early stage and appropriate measures can be taken. As such, this example might serve as a model for other high cost medical procedures in general.

Authors' contributions

AG and KF designed the study and prepared the manuscript. HB was responsible for the data collection, MG for reassembling the data and preparing it for the analysis, and AS and KF performed the data analysis. All co-authors gave advice and contributed to the final version of the manuscript.

Conflict of interest

EBMT is supported by the corporate members as outlined in the funding. There are no personal conflicts of interest to declare.

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